REMARKS

At the outset, Applicants thank Examiner Mertz for her time and the helpful discussion during the interview conducted on June 4, 2003, with the undersigned Applicants' attorney. The substance of the interview is discussed in detail below, with reference to each rejection.

Claim 27 has been canceled without prejudice by the present amendment. Applicants reserve the right to pursue any canceled subject matter in one or more continuing applications. Claims 5 and 29 are allowed. Claims 30 and 32-34 have been amended to recite a specific transporter consensus sequence and GTP/ATP binding motif. New narrower, dependent claims 35-49 have been added. These amendments and new claims are supported throughout the application, e.g., at page 5, lines 23-33, page 9, lines 27-28; page 20, lines 3-5, and by original claim 28, now canceled. No new matter has been added.

Claims 1-7 and 29-49 are pending.

Rejections Under 35 U.S.C. § 112, First Paragraph

The rejection of claims 1-4, 6, 7 and 30-34 for alleged lack of written description and enablement was discussed during the interview of June 4, 2003. As stated in the Examiner's Interview Summary dated June 4, 2003, Applicants' arguments were found persuasive to overcome these rejections. Applicants' arguments are summarized below.

Written Description

In the interview of June 4, 2003, the Examiner found the following arguments persuasive to overcome the written description rejection.

The pending claims fully satisfy the written description requirement under Federal Circuit law and the Patent Office's own Written Description Guidelines (the Guidelines). The Guidelines state that the written description requirement can be satisfied by:

> sufficient description of a representative number of species by actual reduction to practice. . . .or by disclosure of relevant, identifying characteristics, *i.e.*, structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant

was in possession of the claimed genus. (Federal Register, Vol. 66, No. 4, at page 1104).

As discussed with the Examiner, the present claims meet this standard. First, Applicants have disclosed specific, relevant, identifying characteristics of the claimed genus. All the claimed proteins have high sequence similarity to a reference sequence, and function as transporters of organic cations. Second, this function is coupled with a known and disclosed correlation between function and the structure, namely the structure of the transporter consensus sequence disclosed in the specification, e.g., at page 19, lines 24-28, and recited in claims 30, 33 and 34. Third, Applicants have disclosed a multitude of representative species of the claimed genus, as discussed in detail below.

The disclosed transporter consensus sequence provides between 2 and 8 specific substitutions that can be made at each of seven different sites of the 12-residue consensus sequence associated with transporter activity. In addition, the ATG/GTP consensus sequence disclosed at page 20, lines 3-5 provides a further 4 variations (2 each at 2 sites) not counting the 4 Xaa (any amino acid) positions in the middle of this consensus sequence. A consensus sequence is an art-recognized, shorthand way of describing specific, defined, structural functional variations of a sequence having a particular activity, where writing out each and every possible variation would be unwieldy and would convey no additional information. By providing these 2 consensus sequences, Applicants have disclosed what is essentially about 196,000 different species within the claimed genus in addition to the 2 disclosed full length sequences covered by the claims (SEQ ID NO:1 and SEQ ID NO:3). Clearly, Applicants have indeed provided a very large number of representative species of the claimed genus. Accordingly, the present claims satisfy all the conditions for written description provided in the Guidelines.

Moreover, as discussed with the Examiner, the present claims are consistent with the Examples provided in the Synopsis of Application of Written Description Guidelines ("the Synopsis") (available at http://www.uspto.gov/web/menu/written.pdf) for claims that satisfy the written description requirement. In particular, the Examiner is directed to examples 9 and 14 of the Synopsis. Example 14 indicates that a claim to a polypeptide having a specific function and

95% identity to a disclosed sequence is adequately described event though only one representative sequence was disclosed in the specification. Example 9 indicates that a claim to a polypeptide encoded by a nucleic acid that hybridizes under stringent conditions to an identified nucleic acid sequence is adequately described, again even though only one representative sequence was disclosed. The Synopsis indicates that a person of skill in the art would not expect substantial variation among species encompassed within the scope of these claims. In the instant case, Applicants have provided a great deal more than the disclosure of one sequence and its biological function, which disclosure was deemed adequate for written description in Examples 9 and 14 of the Synopsis. As discussed above, Applicants have provided large numbers of exemplary species within the claimed genus. Moreover, both the present specification and many of the present claims recite much more structural information than do the hypothetical specification and claims of Examples 9 and 14 of the Synopsis. See, e.g., the present specification at page 19, line 12 through page 20, line 17, and present claims 6 and 30-49.

In sum, the specification provides ample disclosure of specific, common structural features, as well as functional features, that serve to distinguish the claimed polypeptides within the claims from those outside the claims. Multiple representative species of the claimed genus are disclosed. Accordingly, one of ordinary skill in the art would understand that Applicants were in possession of the full scope of the claims.

Enablement

In the interview of June 4, 2003, the Examiner found the following arguments persuasive to overcome the enablement rejection.

Applicants have provided two specific working examples of the claimed polypeptides: human OCTN1 (SEQ ID NO:1) and human OCTN2 (SEQ ID NO:3). These specific proteins are 76% identical to each other (see the alignment in Figure 3) and function to transport a broad range of organic cations, e.g., TEA, carnitine, mepyramine, quinidine, actinomycin D and pyrilamine (see Figures 8-9). Given this disclosure alone, it would be a routine matter for a skilled person to make numerous functional variants, e.g., by replacing portions of SEQ ID NO:1 with corresponding portions of SEQ ID NO:3, and vice versa.

Even so, the specification provides even more guidance to make and use other functional variants. For example, the specification discloses the sequence of several additional polypeptides in the OCT family, e.g., mouse OCTN1 (SEQ ID NO:22, 54% identical to SEQ ID NO:1), mouse OCTN2 (SEQ ID NO:27, 51% identical to SEQ ID NO:1), and prior art OCT1 and OCT2 (34% identical to SEQ ID NO:1, see page 19, lines 15-17). Although these sequences are not covered by the present claims, they provide a great deal of additional guidance for a skilled artisan to reasonably predict what residues and motifs of the OCT family can be modified while retaining transporter activity. Furthermore, Applicants provide much additional structural information about important parts of OCTN1, including the number and position of 11-12 putative predicted transmembrane domains (Figure 1), the number and position of N-glycosylation sites and the number and position of PKC phosphorylation sites (paragraph bridging pages 19-20). All this information, coupled with the knowledge in the art, could be used by a skilled artisan to reasonably predict, without undue experimentation, what regions of the polypeptides can tolerate changes while still retaining transporter activity. Even if one needed to assay the sequences for transporter activity in order to identify polypeptides of the claims (e.g., using the assays described in Examples 6-8 of the specification), such testing does not rise to the level of undue experimentation. *In re Wands,* 858 F.2d 731 (Fed. Cir. 1988) made it clear that screening for activity to find species that fall within a claim is not undue experimentation where the techniques required for such screening are routine, as is the case here.

A balancing of the Wands factors in the present case supports enablement. The claims, as presently amended, are narrow, being directed to polypeptides having a high degree of structural similarity to the SEQ ID NO:1 and a specific, readily assayable biological activity. The specification provides two working examples and substantial guidance on how to identify polypeptides that have the recited activity. The knowledge and skill in the art for producing the claimed polypeptides is high. With regard to the quantity of experimentation needed, MPEP §2164.01 provides that "the fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation." In the present case, making and using the claimed polypeptides would employ molecular and cell biology techniques disclosed in the specification and routinely practiced in the art.

With regard to the level of predictability in the art, Applicants reiterate that the prior art teaches that "proteins are surprisingly tolerant of amino acid substitutions" (See Bowie et al., 1990, "Deciphering the message in protein sequences: tolerance to amino acid substitutions," *Science* 247:1306-1310, copy enclosed with the response dated December 11, 2003). Based on Bowie's teachings, one can expect to find over half (and possibly well over half) of random substitutions in any given protein results in a protein with full or nearly full activity. Accordingly, the level of unpredictability in the art is not as dismal as the office action suggests. Moreover, to focus the rejection on the "unpredictability" factor of Wands to the exclusion of the other factors is not proper; Wands requires a balancing of all the factors. See MPEP §2164.01(a). On balance, given the specific structural and functional limitations of the claims, the high level of skill in the art, the extensive and detailed guidance provided by Applicants, the disclosure of two full length sequences within the claims, and the routine nature of any experimentation that might be required to make and use the claimed polypeptides, the present claims are clearly enabled.

Although the arguments presented herein apply to all the present claims, as a final matter, Applicant's attorney discussed an additional issue of claim 6 with the Examiner. Applicants noted that claim 6 recites a polypeptide "comprising the amino acid sequence of SEQ ID NO:1, with up to 30 conservative amino acid substitutions." Thus, it was agreed that the statement in the office action that "the claims do not indicate the number of conservative substitutions; i.e., *there is no upper limit* to the amount of substitutions" (emphasis added) is incorrect.

Therefore, Applicants respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. §112, first paragraph.

Rejections Under 35 U.S.C. § 112, Second Paragraph

Claims 30, 33 and 34 are said to be indefinite in the recitation of "transporter consensus sequence." The Examiner indicated that this rejection could be overcome by amending the claims to recite the specific consensus sequence disclosed in the specification. Applicants have done so, and thank the Examiner for this helpful suggestion. The amendments are supported, e.g., at page 5, lines 23-33. Accordingly, Applicants respectfully request withdrawal of the rejection.

In view of the foregoing, Applicants submit that the application is in condition for allowance. The Examiner is kindly requested to contact Applicants' attorney by telephone at 617-542-5070 should any issues remain.

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